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# Meta-analytic-predictive use of historical variance data for the design and analysis of clinical trials☆

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ABSTRACT

Continuous endpoints are common in clinical trials. The design and analysis of such trials is often based on models assuming normally distributed data, possibly after an appropriate transformation. When planning a new trial, information on the variance of the endpoint is usually available from historical trials. Although the idea to use historical data for a new trial is not new, literature on how to formally summarize and use these data on variances is scarce. The meta-analytic-predictive (MAP) approach consists of a random-effects meta-analysis of the historical variance data and a prediction of the variance in the new clinical trial. Two applications that rely on the MAP approach are considered: first, the selection of the sample size in the new trial, guided by the prediction of the variance; and, second, the inclusion of the predicted variance in a Bayesian analysis of the new trial. A clinical trial in patients with wet age-related macular degeneration illustrates the methodology.



## 1. Introduction

Clinical trials with continuous endpoints are common in many disease areas. Examples include blood pressure in hypertension, 6-minute-walk test in heart failure, glycated hemoglobin levels (HbA1C) in diabetes, and lung function parameters such as the forced expiratory volume in one second (FEV1) in asthma or chronic obstructive pulmonary disease (COPD). It is common practice to base the planning and analysis of these endpoints on models assuming (at least approximate) normal distributions, possibly after an appropriate transformation of the data. When designing a new trial, information on the variance of the endpoint is usually available from several historical trials with the same (or at least similar) population and design features as in the new trial. The sample variance and the sample size can typically be extracted for each historical trial. However, literature on how to formally summarize and use these data is limited, with only few exceptions (Pigott and Wu, 2008; Charpentier et al., 2016).

The idea of utilizing historical data for the benefit of a new trial is not new (Pocock, 1976). More recently, Spiegelhalter et al. (2004) described a framework for generalized evidence synthesis integrating data from various sources, whereas Viele et al. (2014), Takeda et al. (2015) and Weaver et al. (2016) reviewed several strategies to incorporate historical control data in clinical trials. In this article, we propose to use a random-effects meta-analysis of the historical variance data to predict the variance in the new trial, based on the meta-analytic-predictive (MAP) framework. The MAP approach has

☆ Code is provided as supplementary material (see Appendix A).

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previously been described in Neuenschwander et al. (2010) and Schmidli et al. (2014) for use in clinical trials with historical control information, but has not yet been considered for predicting the variance. The proposed MAP approach assumes that the variances in the historical trials and the new trial are similar rather than identical. Some degree of between-trial heterogeneity may be expected, as differences in trial design and conduct always occur; see, for example, Mittlboeck and Heinzl (2006) and Higgins et al. (2009).

Two application areas in designing and analyzing clinical trials with normal endpoints are considered. First, information on the variance of the endpoint is important for the design of a new trial, in particular for the determination of the sample size. For many trial designs, the sample size is proportional to the assumed variance, using classical sample size formulas; see for example Julious (2004b). Hence, the prediction of the variance in the new trial provided by the MAP approach can guide the selection of the sample size, which will be described both from a Bayesian and classical perspective. Second, in a Bayesian framework, information on the variance can also be included as prior information in the analysis of the new trial; see for example Box and Tiao (2011). This is of particular interest for small trials in rare diseases, proof-of-concept trials, or pediatric settings. Here we describe how the proposed MAP approach can inform the choice of prior distributions for the variance in Bayesian analyses. To our knowledge, the systematic summary of historical variance information and its formal use for clinical trial design and analysis has not been considered yet.

We will focus on the most common clinical trial design, where patients are randomized to a test treatment and to control, with the aim to show that the test treatment is superior. However, our approach is relevant for other types of trials, such as non-inferiority, equivalence, crossover or dose-finding trials.

As a case study we consider a proof-of-concept (PoC) trial in wet age-related macular degeneration (AMD), which is among the leading causes of vision loss. The most relevant clinical endpoint in trials with AMD patients is visual acuity. In the analysis, this outcome is typically taken as normally distributed. While confirmatory trials in AMD involve hundreds of patients per group, and last one to two years, exploratory trials are much smaller and shorter. For example the trial by Brown et al. (2011) had a core phase of three months and about 30 patients per treatment group.

The article is structured as follows. Section 2 describes the MAP approach for variances. Section 3 explains how to use the results for trial design and analysis. In Section 4, a detailed clinical trial example illustrates the methodology. Section 5 contains the discussion. Code for implementing the MAP approach for variances is provided as supplementary material (see Appendix A).

## 2. Meta-analytic-predictive (MAP) approach for variances

For the design and analysis of a new clinical trial with normally distributed endpoint, information on the variance is important. This information typically comes from historical trials in the same or similar population and with the same endpoint as in the new trial. Suppose that $J$ relevant historical studies are available, from which the sample variances and sample sizes can be extracted. We assume the distribution of the sample variance from the $j$th historical study is

$$s_j^2 \mid \sigma_j^2 \sim Gamma(0.5\nu_j, 0.5\nu_j/\sigma_j^2), \tag{1}$$

or, equivalently $\nu_j s_j^2/\sigma_j^2 \sim \chi^2_{\nu_j}$, with degrees of freedom $\nu_j$ and variance $\sigma_j^2$, for $j = 1, \ldots, J$; $\chi^2_\nu$ denotes the chi-squared distribution. The $Gamma(a, b)$ distribution is parametrized by the shape and rate parameters $a$ and $b$, and has expectation $a/b$ and variance $a/b^2$. The variance in the new trial is denoted by $\sigma_\star^2$.

In the following, it will be more convenient and natural to work with the log-transformed variances, $\theta_j = \log(\sigma_j^2)$, $j = 1, \ldots, J, \star$. The transformed parameters are then defined on the whole real line, and the likelihood in (1) is exactly data-translated for $\theta$, i.e. the shape of the likelihood is unchanged for different values of the sample variance; see Box and Tiao (2011). Also, for large sample sizes $n$, the maximum-likelihood (ML) estimator of $\theta$ and the posterior distribution of $\theta$ with vague prior have the particularly simple variance $2/n$; see Gelman et al. (2014).

In order to learn from the historical trials, the variances $\sigma_\star^2, \sigma_1^2, \ldots, \sigma_J^2$ have to be linked. An extreme view would consider these parameters to be all equal, which would allow us to pool the historical data. It seems more realistic to consider parameters to be similar but not identical. This can be expressed by hierarchical (random-effects) models which have a long history of successful use in meta-analysis and evidence synthesis; see Spiegelhalter et al. (2004) and Sutton et al. (2012). The normal hierarchical model for log-variances is

$$\theta_\star, \theta_1, \ldots, \theta_J \mid \mu, \tau \sim N(\mu, \tau^2), \tag{2}$$

with mean $\mu$ and between-trial standard deviation $\tau$. The model may be extended by including trial-level covariate information, or using a different random-effects distribution. Model (1), (2) allows us to summarize the historical variance information, and to predict the variance $\sigma_\star^2$ in a new study.

The between-trial standard deviation $\tau$ quantifies how similar the variances in the different studies are. For very small values of $\tau$, the variances are almost identical, while for very large values of $\tau$ the variances are essentially unrelated. The between-trial standard deviation $\tau$ is best interpreted relative to the large sample standard deviation of the ML estimator $\hat{\theta}$ (or of the posterior distribution for $\theta$), scaled to one observation, which is $\sqrt{2} = 1.4$. Using a similar categorization as in Neuenschwander et al. (2010), $\tau$ values of 0.09, 0.18, 0.35, 0.7, 1.4 can be interpreted as small, moderate, substantial, large and very large between-trial heterogeneity. Table 1 shows that for large $\tau$ almost nothing can be learned on the variance in a new trial, even if many big historical trials would be available (i.e. if $\mu$ and $\tau$ are essentially known).

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